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DBI

Phenformin (DBI-U.S. Vitamin), a biguanide, is a new oral hypoglycemic agent differing in both chemical structure and mode of action from the sulfonylurea compounds, tolbutamide (Orinase) and chlorpropamide (Diabinese). Unlike these compounds, DBI does have some effectiveness in juvenile-type diabetes.

SIDE EFFECTS - No serious toxicity of any kind has thus far been encountered in fairly extensive clinical trials of DBI. On the other hand, such side reactions as loss of appetite, metallic taste, nausea and diarrhea have been so frequent as to limit seriously the usefulness of the drug. These side effects are dose-related; they can apparently be prevented or reduced in some cases by initiation of treatment with very small doses, with the gradual addition of small increments. In many cases, however, the side effects appear with doses so low as to preclude effective use of the drug. Ill-defined malaise and weakness may occur even in cases otherwise satisfactorily controlled by DBI, with rapid improvement on reversion to insulin.

The claim is made that DBI "lowers elevated blood sugar and eliminates glycosuria in mild, moderate and severe diabetes." The drug has been found effective in many stable adult diabetics, but these can generally be as well controlled with Orinase, and with much less likelihood of unpleasant side effects. It is also claimed that DBI often permits satisfactory regulation of diabetes in patients who have not responded initially to other oral therapy or who have become resistant to it. DBI appears to be effective in a very small number of such cases, especially when it is used to supplement rather than to replace other oral therapy.

Unlike the sulfonylureas, DBI has a hypoglycemic effect in some diabetic children and in some adults with unstable diabetes when it is used as a supplement to insulin. The drug has been recommended for use in conjunction with insulin to stabilize unstable or "brittle" diabetes and to reduce the insulin requirement; evidence in support of these claims consists largely of clinical impressions. The use of DBI solely to reduce insulin requirement affords no advantage in convenience, cost or safety.

DOSAGE - As with the sulfonylureas, there is no relationship between the amount of insulin a patient requires and the required dosage of DBI. Though some patients may tolerate 150 mg. or even more daily in divided doses, some

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have trouble from half that much. It is probably safest to start with 25 mg. three times a day, building up the doses gradually to the point where the diabetes is controlled or side effects stop the use of the drug. If the attempt is made to substitute DBI for insulin, the insulin dose should be lowered gradually, with control by frequent urine testing. Except in patients with mild diabetes, the attempt will seldom succeed.

While DBI is apparently a safe drug, and one that may occasionally be effective in juvenile diabetes, Medical Letter consultants feel that it should still be regarded as in the stage of clinical trial.

RAUWOLFIA PRODUCTS IN HYPERTENSION

The voluminous literature on the oral use of rauwolfia products in the treatment of hypertension shows sharply conflicting opinions on the value of these drugs. It is true that large doses of reserpine given intramuscularly may produce dramatic results in hypertensive crises; but the benefits of oral dosage in chronic hypertension are less clear.

Most of the studies with rauwolfia products in hypertension have been uncontrolled, or inadequately controlled, and have failed to take into account placebo and other psychological effects in reducing blood pressure. To attribute a reduction of blood pressure in mild hypertension to a drug alone is to underestimate the therapeutic value of repeated contact between patient and physician in a disorder in which emotional factors play such a significant role.

EFFECTIVENESS OF THERAPY - In one careful study (G. Perera, Symposium on Hypotensive Drugs, Wellcome Foundation, 1956, p. 121) of 30 patients with uncomplicated hypertension, only 11 responded with a fall in blood pressure that could be attributed to reserpine (0.25 mg. twice a day) or the whole root (50 to 100 mg. twice a day). In a detailed study by A. R. Krogsgaard (Acta Medica Scand., 162:449, 1958), of 75 patients only eleven, most of them with milder forms of hypertension, showed a satisfactory response to an average maintenance dose of 0.5 mg. of reserpine. Twenty-seven per cent of the patients in this series had to stop therapy because of side effects. The author makes the pertinent comment on reserpine therapy that "there can hardly be any doubt that the more critical the investigation the smaller the number of patients who will fulfill the criteria of a satisfactory result." Shapiro and Teng (N. E. J. of Med., 256:970, 1957) observed that doses of 2 mg. of the rauwolfia derivative, alseroxylon, three times daily caused an average decrease in diastolic blood pressure 10 millimeters greater than a placebo but only five millimeters greater than phenobarbital.

In general, it appears that, at most, from a third to a half of patients with mild, uncomplicated hypertension can be expected to respond with a modest fall in blood pressure. It is well known, however, that mild, uncomplicated hypertension has a good prognosis without drug therapy (M. J. D. Newman and J. I. S. Robertson, British Med. J., 5/30/59, p. 1368). Furthermore, despite the extensive literature on rauwolfia products, it has not been shown that the prognosis in mild essential hypertension is improved by a modest fall in diastolic pressure.

In moderate, severe and malignant hypertension, that is, in patients with a diastolic pressure consistently above 110 mm. of mercury or with evidence of cardiac, renal, cerebral or retinal complications (and particularly in the male patient, whose prognosis is worse than that of the female patient), hypotensive drug therapy is indicated, and is effective in controlling symptoms and improving prognosis. Oral rauwolfia products are seldom useful by themselves in the treatment of severe hypertension, but are often helpful in combination with other hypotensive drugs such as hydralazine and ganglion blockers.

SIDE EFFECTS - The mild hypotensive action of rauwolfia products is frequently purchased at the cost of disturbing and sometimes serious side effects. The most common side reactions of the rauwolfia products are nasal congestion, nosebleed, diarrhea, nightmares and lethargy. More serious reactions, including emotional depression and fluid retention, also occur. A recent Mayo Clinic study (R. M. Quetsch, et al., Circulation, 19: 366, 1959) noted the occurrence of depression in 26 per cent of a group of rauwolfia-treated patients, and in 50 per cent of such patients who had a prior history of depression. Seven per cent of the treated patients had depression severe enough to lead to hospitalization or to attempted suicide. The average dose of reserpine was 0.53 mg. per day for the entire series, 0.62 mg. for those who developed depression; this side reaction was not noted with dosage of less than 0.2 mg. per day. The action of the drug was insidious, with onset of depression occurring after an average of five months of treatment. Numerous other reports show depression, often serious, from rauwolfia therapy. Furthermore, rauwolfia-induced depression can continue for months after use of the drug is stopped ("Current Concepts of Therapy," N. E. J. of Med., 260: 766, 1959).

Medical Letter consultants stress that with continued rauwolfia therapy, not only should the patient be carefully observed, but the family as well as the patient should be alerted to report the appearance of depression, with immediate discontinuance of the drug if signs of depression appear. Normally, most patients will not realize that delayed side reactions, particularly depression, are connected with the drug, and such reactions may never be reported to the physician.

OTHER RAUWOLFIA PRODUCTS - Besides reserpine, rauwolfia alkaloids or fractions promoted as hypotensive agents include alseroxylon (Rautensin-Dorsey; Rau-Tab--National; Rauwiloid-Riker), deserpidine (Harmonyl-Abbott), rescinnamine (Moderil-Pfizer) and syrosingopine (Singoserp-Ciba). Although some investigators have reported a lower incidence of side effects with these products than with reserpine, significant differences in the incidence of mental depression with equi-potent hypotensive doses have yet to be established by carefully controlled trials.

If reserpine or any other rauwolfia product is used, minimum doses should be prescribed. To insure against long-continued, unsupervised use of the drug, prescriptions should not be renewable. Large initial doses are sometimes recommended, but they are of doubtful merit. Daily maintenance doses are variously stated as 50 to 200 mg. for the whole root, 2 to 4 mg. for alseroxylon, 0.1 to 1 mg. for reserpine, 0.1 to 2 mg. for rescinnamine and deserpidine, and 0.5 to 3 mg. for syrosingopine.

ENZYME TESTS FOR URINE SUGAR

Clinistix (Ames) and Tes-Tape (Lilly) are test papers for glycosuria which need only be dipped into the urine sample and read after one to two minutes. No heating or other manipulation is needed. Both papers employ the enzyme glucose oxidase with orthotolidine as an indicator. Unlike the conventional copper reduction tests, such as Benedict, Fehling and Clinitest, these papers are specific, giving a blue or green to blue-black color only with glucose. Since they are also convenient, they offer an excellent means of screening large groups for diabetes.

RELIABILITY OF TESTS - While the test papers are also helpful in the management of diabetes, an understanding of their limitations is important. Clinistix, according to the manufacturer, "determines if sugar is absent or present; and, if present, roughly indicates whether it is in large or small amounts." Tes-Tape is claimed to give accurate quantitative determinations of glucose in concentrations up to 2 per cent. In the experience of Medical Letter consultants, test papers cannot be relied on for consistently accurate quantitative readings. To the unpredictable error inherent in the method must be added the inability of many patients to match colors accurately and the tendency of some to err on the side of under-reading for psychological reasons.

Directions must, of course, be followed carefully. The strip should be dipped, and not left immersed, since the reaction requires oxygen. The user should be aware that the enzyme can be inactivated by heat, moisture, sunlight, or prolonged storage; although improvements in both the products and the packaging have reduced the importance of these factors, it is still advisable to avoid storage in such a place as a warm, moist bathroom. Changes in Tes-Tape, as well as the instruction to wait two minutes to make the final reading when the one-minute color change indicates 0.5 per cent sugar, have undoubtedly improved accuracy in the high range, but they do not insure consistently correct differentiation of higher sugar concentrations. While Medical Letter consultants have found that reliance on test papers in the management of severe diabetes can be hazardous, the hazard can be minimized if the patient is instructed to use Benedict's solution or Clinitest Tablets (Ames) when the Tes-Tape indicates 0.5 per cent or more of glucose, or the Clinistix shows medium or dark color. In general, it is reasonably safe to rely on a reading only when it clearly indicates less than 0.5 per cent glucose.

In summary, these agents are useful and reliable for mass screening for diabetes, and for following patients with mild diabetes. Because they are specific for glucose, they simplify the differentiation of glucose from lactose, an important point, since harmless lactosuria, renal glycosuria, and true early diabetes are all fairly common in late pregnancy. These agents also serve to differentiate other sugars from glucose in the urine, thus eliminating unnecessary blood-sugar testing. The papers cannot, of course, aid in differentiating diabetes from benign glycosuria. The cost of the papers is about 1.5 to 2 cents per test.

COMBINATION TESTS - Uristix (Ames) provides a strip test for glucose and protein in a single dip. Another new product, Combistix (Ames), permits simultaneous determination of urine glucose, protein and pH.

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